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A GENERAL VIEW OF CANCER RESEARCH*

The Fourth James Ewing Memorial Lecture

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SOME years have passed since cancer patients and the medical profession last benefited by direct association with Dr. James Ewing. Yet those who knew him (and there are many of us present who did) surely retain a vivid impression of his personality and genius, which seem to transcend time. My words could add nothing to your experience. Those who did not have the fortune of his acquaintance may know him as a legend—as one who devoted the major part of his life to the study and diagnosis of cancer; as scholar, author, teacher; and as one of the scientific founders of Memorial Hospital. Such a conception is a true one. But legendary figures, as they grow in repute, may dwindle in humanity—become less real. So rather than discuss his work, I should like only to say, of the man himself, that James Ewing was intensely human—incisive, sincere, altruistic—one who sought truths, and found them, in the study of human nature as well as disease. No lines in epitaph could be more fitting than those of Lowell:

Great truths are portions of the soul of man;
Great souls are portions of eternity.

* Delivered at the Stated Meeting of The New York Academy of Medicine, May 5, 1949.

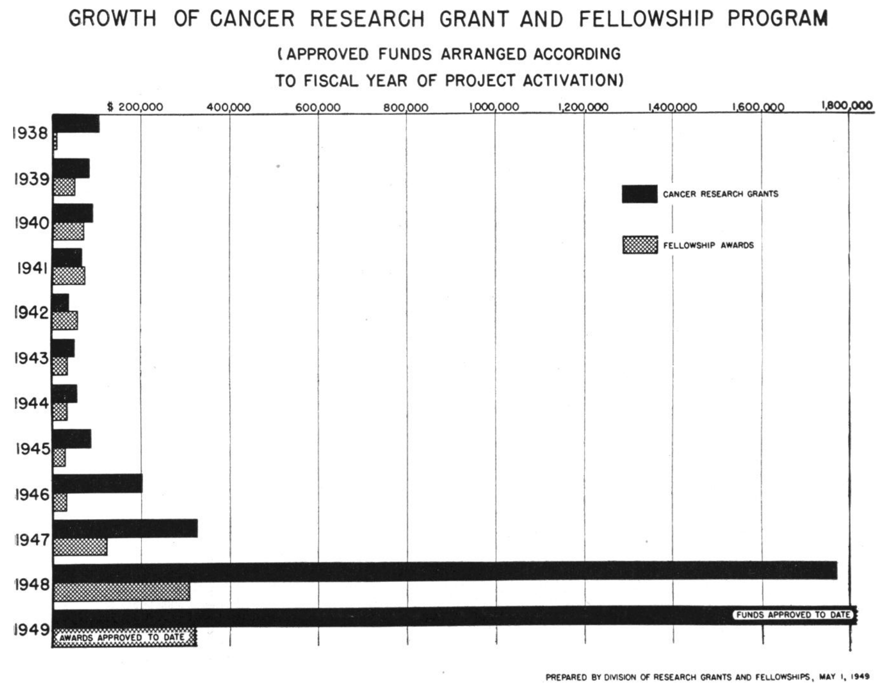


Chart 1

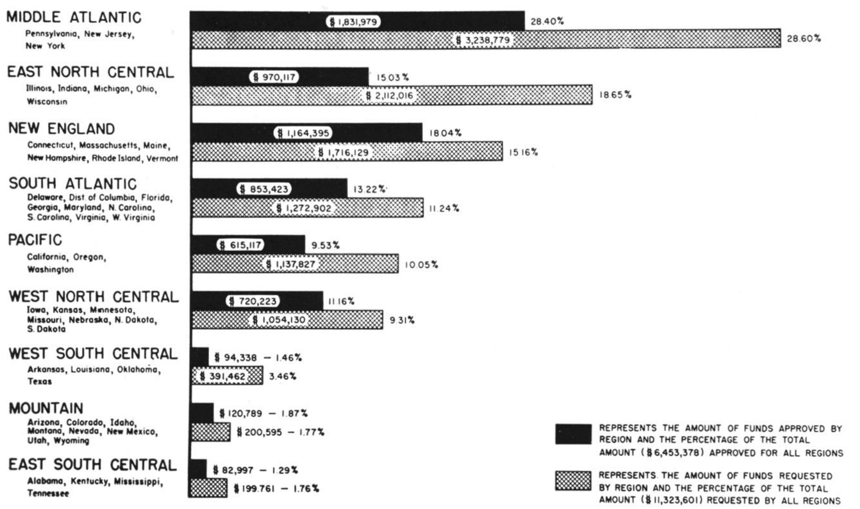
To have been asked to speak tonight before this group, assembled in memory of Dr. Ewing, is indeed an honor.

Dr. L'Esperance, in her cordial invitation, suggested the theme of cancer research and the Public Health Service program in this field. The subject seems particularly appropriate in view of the growth of cancer research in recent years, largely as a result of the mounting interest of the American public and medical profession, the rising hope that research will ultimately defeat this disease, and the augmented role of the American Cancer Society and the Federal Government in the national cancer research movement.

I should like, first, to describe briefly the Federal cancer research program. In the early 1920's two groups of United States Public Health Service scientists—one in Washington, D. C., the other on the campus of Harvard University—initiated projects in this field. Under the National Cancer Act of 1937, these groups were merged to form the nucleus of the National Cancer Institute. This is one of the National

GEOGRAPHIC DISTRIBUTION OF
NATIONAL CANCER INSTITUTE RESEARCH GRANT FUNDS
IN PROPORTION TO REQUESTS

1937 THROUGH APRIL 30, 1949



Prepared by Division of Research Grants and Fellowships, May 1, 1949

Chart 2

Institutes of Health, the principal research branch of the Public Health Service. As many of you know, the research of the Cancer Institute is conducted, for the most part, in two well-equipped buildings, completed in 1939 and early 1948 at Bethesda, Maryland.

The research at Bethesda, however, is only a small part of that financed by the Government through the Institute. I refer now to the Federal program of grants to support cancer investigation in outside institutions, a new venture of the Public Health Service when the Institute was established. This program is conducted with the advice of a National Advisory Cancer Council, provided by the National Cancer Act. The Council is composed of six leading non-Government authorities in cancer, who serve three-year terms. It advises on Institute plans and policies, and reviews and makes recommendations on grant-in-aid applications. The Surgeon General, as Council chairman, is in turn authorized to make the grants.

NATIONAL CANCER INSTITUTE RESEARCH GRANT FUNDS APPROVED IN RELATION TO THOSE REQUESTED BY REGION

1937 THROUGH APRIL 30, 1949

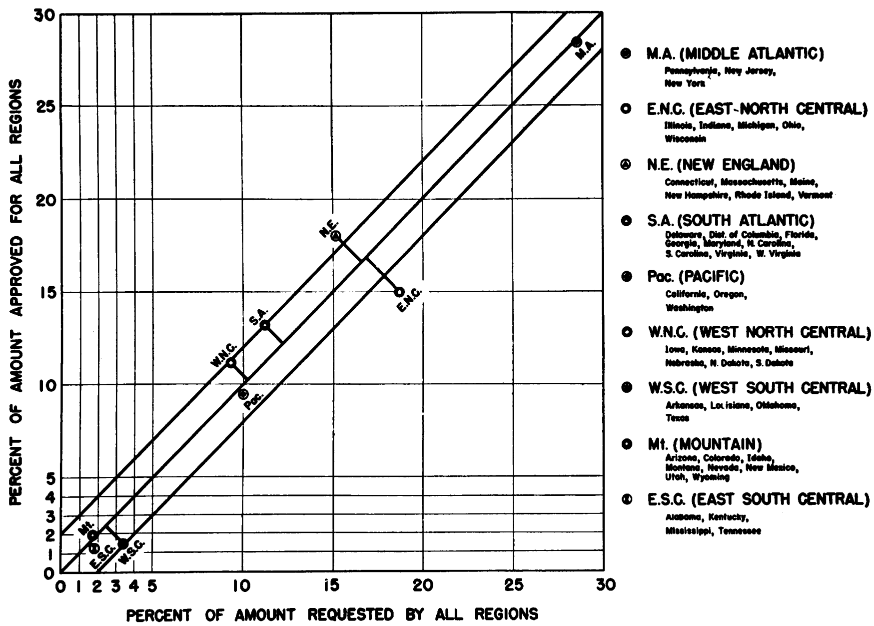


Chart 3

The growth of the grant-in-aid program is represented in Chart 1. Each black bar shows the total amount granted that year for cancer research in nonfederal institutions, and the shaded bars represent the amounts awarded for research fellowships. It should be pointed out that the bars represent projects started each year, and taken singly do not necessarily reflect annual Congressional appropriations, though in the aggregate they do. Research fellowships are awarded to increase the number of scientists trained in disciplines through which the cancer problem can be attacked. On the first of May 1949, there were 100 National Cancer Institute research fellows in active training in the United States and abroad.

Chart 2 presents a geographic distribution of cancer research grants and requests since the inception of the program. Other data indicate that this material reflects, quite accurately, the distribution of all

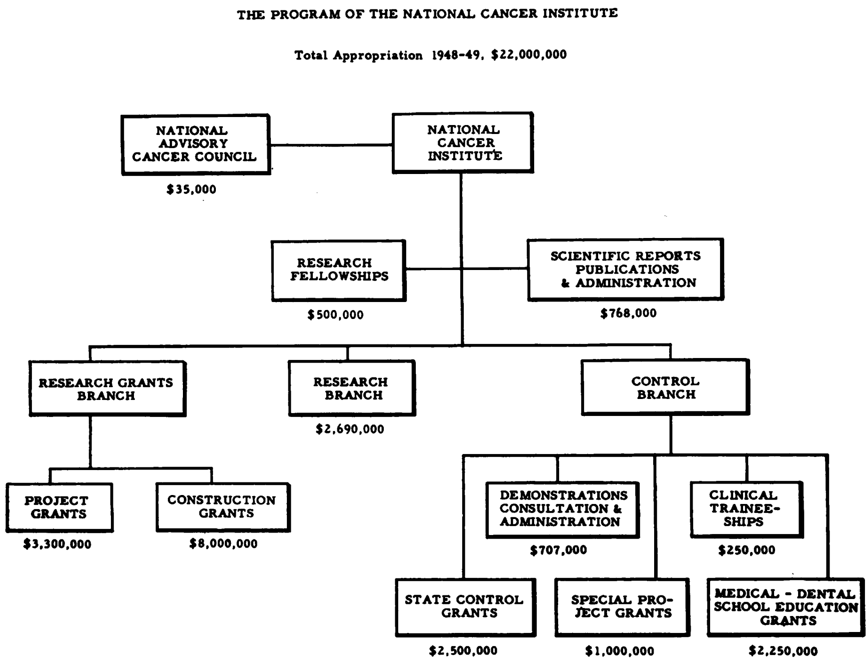


Chart 4

cancer research and 'research potential' throughout the country. For the past two years, grants for the construction of research facilities (not shown in this chart) have helped to increase the research potential of the less active areas.

The same data were used in preparing Chart 3, which presents a comparison of the amount awarded and that requested, by region. Only the applications the Council has acted on are represented: some requests have been withdrawn and a few await further investigation. The proximity of plotted points to the diagonal line reflects a nearly constant ratio of approved to requested grants.*

In 1947 the National Cancer Institute was reorganized to provide for effective integration of a much-expanded program. Chart 4 shows the allotment of appropriation for the fiscal year 1949. It shows that the activities of the Institute are administratively divided into three major fields—research grants to outside institutions, scientific research

* Deviation is greatest for the Southwest, which made only a few applications, and those for large sums.

within the Institute, and cancer control. Of the total appropriation of $22,000,000 for this year, more than half, $11,300,000, has been allocated for research grants—$8,000,000 of that, for construction of cancer research facilities. About twelve per cent of the total appropriation, $2,690,000, will be spent on intramural research; and about thirty per cent, $6,707,000, on cancer control.

If these activities were presented in detail, they would illustrate the breadth of the cancer research field—the diversity of approaches, the multiplicity of disciplines applied to fight this disease. No stronghold against science is under a more varied attack. In the remainder of my paper, I have tried to present a general view of the scientific problem posed by cancer. And now, in the hope that this view will be of interest, I should like to discuss in relatively nontechnical terms, the investigative aspects of cancer research.

Pasteur, in defining *science*, wrote that it is "built up of successive solutions given to questions of ever-increasing subtlety, approaching nearer and nearer towards the very essence of phenomena."[1] This statement seems especially applicable to cancer research. Nearly every method whereby other diseases were controlled has been tried—serologic techniques, the search for a microörganism, a decisive dietary factor, a curative drug. Some of these approaches, of course, still hold promise; but refinements inconceivable to the early workers seem necessary. We must continue to answer "questions of ever-increasing subtlety."

Consider, for instance, the matter of etiology. With the discovery, in many diseases, of a causative microörganism or its vector, the problem of control was well in hand. Other diseases were found to result from a dietary deficiency, and still others followed a simple genetic pattern. For all practical purposes, the discovery of a cause closed the question of etiology. In the study of cancer, however, investigation has disclosed a gamut of etiologic agents and influences. Let me enumerate briefly: energy agents, such as X-rays, radioactive substances, ultraviolet rays, and heat; more than 300 chemical compounds; viruses; parasites (which may be vectors for viruses); endocrine and dietary manipulations; and multiple genetic factors.[2] We are at liberty to regard cancer as one disease with a variety of possible causes, or as a number of diseases.

To know ways to produce cancer is by no means to have found 'the cause,' for most tumors are not attributable to known carcinogens.

And if subtlety is in order, it may be said that the purpose of studying cancer etiology is no longer to find the cause, but to *explain the origin.*

A large part of cancer research in this country and abroad is devoted to the study of tumor genesis and early development, since elucidation of these processes would, in all probability, lead not only to preventive measures but also to improved diagnosis and therapy. This may be the long way, but it seems sure. In discussing studies of origin and development, I shall observe a broad classification into fundamental biologic investigation and studies of carcinogenic agents and influences.

Although the term *cancer* is usually associated with a complex of phenomena, including invasion, metastasis and other aberrations of growth, the most prominent characteristic of the disease is the excessive, inexorable proliferation of cells. That characteristic is well recognized: I mention it only to illustrate that cancer is a disease of the mechanism whereby tissues are formed or replenished—the forces controlling the type of cells engendered and the direction and cessation of growth. In this light we see clearly the importance of investigating basic biologic processes, such as cell division, differentiation and adaptation.

In recent years the intracellular movements involved in mitosis have been investigated in terms of tension resulting from changes in the viscosity of protoplasm. Studies by Chalkley, Marsland and others indicate that cell division depends, to some extent, upon colloidal fluctuations between sol and gel.[3] One can hope that the fluctuations will in turn be explained. But the problem, it would seem, approaches a basic physical level, where it can be studied in terms of factors affecting colloids, such as pressure, temperature and chemical composition.

During the past decade, the intracellular microcosm has been under exploration with the electron microscope, which is about a hundred times as powerful as previous instruments. Recent studies by Porter and others have disclosed entities that may represent the underlying structure of cytoplasm.[4] In combination with ultracentrifugation, ultrafiltration and other newly developed techniques, the electron microscope may yet reveal characteristics of the cancer cell that will elucidate its origin and activity.

The processes of differentiation and regeneration are studied because of possible similarities to carcinogenesis and subsequent anaplasia. Both differentiation and carcinogenesis apparently result in a new type of cell. The former process, however, is consistent with the total pattern of cellular organization—it is controlled; whereas in carcinogenesis, the part defies the whole. The processes may also differ in direction: that is, the cells in differentiation become, as a rule, more specialized; whereas in tumors they seem to dedifferentiate, to form tissues more like each other, morphologically and chemically, than were the tissues of origin.[5,6] It appears, however, that dedifferentiation may also occur in noncancerous development. In lower forms such as Amphibia, regeneration, as in a healing wound, is reported by Rose to involve dedifferentiation as a primary stage;[7] and in tissue culture morphologic simplification has been observed by Fischer and others in cells of even higher vertebrates.[8] Whether controlled dedifferentiation occurs, however, *in vivo* in higher animals, such as man, is still unknown.

To explain the relation of differentiation to cancer, much basic information is needed. We should like to know, for instance, whether the level of differentiation influences susceptibility of the cell to carcinogens. Clarification of the identity and role of 'organizers' would be valuable. In these and other basic biologic investigations, lower forms lend themselves well to study: the planarian, noted for its remarkable ability to regenerate a head; the hydra, whose cells after passage through a strainer will reassemble to form whole animals; the platy fish [Platypoecilus], because of its wide regenerative capacity, its response to androgen, and its susceptibility to melanoma in certain hybrids. Studies of differentiation represent attempts to relate carcinogenesis to the source of cellular variation, a process of which far too little is known.

One type of cellular variation is represented in adaptation to an unfavorable environment. Many scientists believe that all living organisms, including the cells of a multicellular species, are endowed with a capacity to adapt. This suggests a point of view from which cancer may be regarded. Carcinogenesis may be the manifestation of an attempt of cells to survive through adaptation. From the standpoint of the host, cancer certainly represents the antithesis of a tendency toward survival; but we cannot deny that a cancer cell, among its normal neighbors, is an exalted being. And one could add that its destruction of the host does not debase the concept: some microörganisms do the same. Experiments by Spencer[9,10] suggest that processes similar to some found in cancer occur in single-cell species exposed to carcinogens over many generations. Exposure of paramecia to methylcholanthrene enhanced the subsequent survival value and population levels, and bacteria tended to adapt to heat when early exposure was rhythmic, but perished when it was continuous. These transformations are readily accepted as adaptive.

In the field of basic biologic investigation, notable advances have been made recently by some of our workers in tissue culture. Earle and Evans at the National Cancer Institute have worked out a technique for growing cells under a sheet of perforated cellophane, which obviates the need for a plasma clot and affords much larger cultures than were previously grown.[11]

A further accomplishment of this laboratory, by Earle and Sanford, is a procedure that allows, for the first time, the growth of an isolated cancer cell *in vitro*.[12] These techniques, in combination, make possible the growth of large cultures from a single cell, and consequently the cancer research worker can now study ample cultures of uniform cellular origin and type.

Obviously these achievements increase greatly the applicability and quantitative accuracy of tissue culture as a means of studying possible chemotherapeutic agents, carcinogenesis, and cell variation, migration and growth rate. The new techniques are already being used in an effort to define more accurately the nutrition of the cancer cell. The full potentiality of these advances, however, cannot be estimated at the present time.

A discussion of carcinogenic agents and influences may well begin with the subject of radiation, since the first experimental cancers in animals, such as Clunet[13] reported in 1910, were induced with X-rays. On the basis of numerous experiments and clinical observations, investigators agree that ultraviolet and ionizing radiations are carcinogenic. The mechanism of radiation injury is only partly understood. Experiments indicate, however, that absorption of radiation causes chemical changes detrimental to cells and tissues. The biologic effect is to some degree cumulative. And therein lies the danger of repeated exposure, even to very small doses. In studies by Lorenz and others,[14] chronic whole-body irradiation hastened the onset of cancer in mice predisposed to the disease, and late effects other than tumor production include shortening of the life span. X-ray diagnosis in the hands of a competent physician constitutes a justifiable exposure. The problem of radiation injury, however, is becoming more and more important with the increasing use of ionizing radiations in science and industry.[15]

TABLE I*—HIGHLIGHTS IN THE STUDY OF CHEMICAL CARCINOGENS

Investigator	*Contribution*
Pott (1775)	Reported soot-induced carcinomas in chimney sweeps
Yamagiwa, Ichikawa (1915)	Produced carcinoma of rabbit's ear with tar
Kennaway, Cook, Hieger (1930)	Isolated 3,4-benzpyrene from coal tar; synthesized other carcinogens
Shear, Andervont, Fieser, Lorenz, Stewart (1930—)	Studied administration and effects of carcinogenic hydrocarbons on animals of inbred strains
Wieland, Cook (1933)	Prepared 20-methylcholanthrene from desoxycholic acid
Yoshida, Sasaki (1934)	Produced hepatomas in rats with *o*-aminoazotoluene
Edwards (1941)	Produced hepatomas in mice with carbon tetrachloride
Wilson, De Eds, Cox (1941)	Noted multiple tumors in rats fed N-acetyl-2-aminofluorene
Nettleship, Henshaw (1943)	Noted that urethan increased lung tumors in predisposed mice
Berenblum (1941)	Discovered synergy of 3,4-benzpyrene and croton oil

* Material from Greenstein, J. P., *Biochemistry of Cancer,* New York: Academic Press, Inc., 1947.

Table I gives a thumbnail history of the chemical carcinogens. Sir Percival Pott is credited with the first report of industrial cancer.—During the 19th century, skin cancer was prevalent among workers in the coal tar industry; but many years passed before two Japanese workers proved experimentally that tar is carcinogenic.—The next step was to isolate a pure carcinogen, and this was finally accomplished through the perseverance of Kennaway's group in England.—As these workers produced other pure agents, a group established by Shear, under the United States Public Health Service, studied the carcinogenicity of compounds synthesized in this country, and for about a decade the two major efforts in the field overlapped.—In view of the next achievement listed (the preparation of a potent carcinogen from bile acid), one naturally wonders whether this or a similar transformation could occur in the body. Biochemists agree that *this* transformation is highly improbable; but the close structural relation of many carcinogens and

TABLE II*—HIGHLIGHTS OF TUMOR VIROLOGY

Investigator	*Source of Virus*	*Subject and Result*
Rous (1911)	Plymouth Rock hen, sarcoma	Same species, sarcoma
Ellerman (1918)	Chicken, leukemic blood	Same species, leukemia
Shope (1932)	Cottontail rabbit, papilloma	Cottontail, domestic rabbits; papilloma
Rous (1935)	Shope papilloma	Domestic rabbit, carcinoma
Bittner (1936)	Mice of high tumor strain, milk	Progeny, mammary carcinoma
Lucké (1938)	Leopard frog, carcinoma	Sames species, carcinoma of kidney
Duran-Reynals (1942—)	Rous sarcoma	Duckling and other birds; variety of tumors

* Material from Oberling, C., *The Riddle of Cancer,* New Haven, Yale Univ. Press, 1944.[16]

naturally occurring substances, such as the steroid hormones, demands that the possibility of a similar conversion be considered.

—The next three lines represent the introduction of new groups of compounds.—Urethan, mentioned in the next to the last line, offers relative simplicity of structure, a decided advantage in tracer studies of the mechanism of carcinogenesis. Larsen, studying the structure of compounds of this type in relation to biologic response, found that the simplest alterations of the urethan molecule reduced activity fully 90 per cent. Urethan administered to pregnant mice induced lung tumors in the offspring.—And lastly, we have a clear-cut example of synergistic action between a carcinogen and a noncarcinogen, a phenomenon discovered about ten years ago by Shear, who showed that the basic fraction of creosote oil accelerated skin tumor production by various hydrocarbons. Berenblum, now at the National Cancer Institute on a Special Fellowship, has shown that the appearance of cancer in mice following application of benzpyrene, the 'initiator,' is markedly accelerated by croton oil, a noncarcinogen acting as 'promoter.'

Over the years much thought has been spent in searching the chemical and other carcinogens for a characteristic structure or mode of action—in short, a 'common denominator.' Perhaps the oldest and most familiar deduction is the 'irritation hypothesis,' extant today in modified forms. The chemical carcinogens especially have been subjected to this analysis, which largely accounts for their multiplicity; but by and large, they remain in structurally unrelated groups. In recent years, emphasis in the search for a common denominator has shifted to the cell.

Table II outlines the study of virus tumors. Rous was among the first to succeed in transmitting cancer from one animal to another by means of a cell-free filtrate.* The Rous agent has increased in virulence with subsequent transfers, and will now induce cancer in chickens within five days after inoculation, about ten times as rapidly as the most effective of other carcinogens.—Ellerman, using filtrates of sera from fowl, transmitted leukemia within the species.†—The benign virus tumor found by Shope in the wild rabbit—was shown by Rous, Beard and Kidd to become malignant in domestic rabbits.—Next in the table is Bittner's demonstration that mice of a strain in which mammary carcinoma is ordinarily frequent develop few tumors if nursed by mice of a low-tumor strain, indicating that a factor of mammary tumor development in mice is transmitted by the milk. The history of the milk agent is too long and involved to review at this time.

—To my knowledge, the tumor of the frog shown by Lucké has not been transmitted by a cell-free inoculum, but results were obtained with grafts killed by storage in glycerol.—Lastly, Duran-Reynals's studies in virus variation: showing, for example, that the Rous agent, though innocuous to ducks, will 'take' in ducklings, and when recovered from a late tumor will then take in ducks, but will have lost capacity to induce cancer in chickens. In short, a tumor virus specific for one species may become specific for another, if closely related. It will be noted that in every example in the table (except that of the milk factor in mice) inoculation has been necessary to transfer the disease.

Round shadow-casting particles, believed to be viruses of the Shope papilloma, have been photographed by Kahler and others with the electron microscope. This agent cannot be recovered from the carcinoma it induces in the rabbit, though serologic methods have demonstrated its presence. It is said to be 'masked.' At present, one objective in tumor virology is to develop unmasking techniques, which would then be applied to other tumors in an effort to reveal a virus if one exists.

* Fujinami and Inamoto, at about the same time, reported cell-free transmission of a myxosarcoma of fowl.

† A similar disease in fowl, a malignant leukosis, is also attributed to a filterable agent, and recent studies by the U. S. Department of Agriculture indicate that leukosis may be contagious in birds.[17]

Table III*—HIGHLIGHTS OF TUMOR ENDOCRINOLOGY

Investigator	*Contribution*
Marie (1886)	Associated cases of acromegaly with pituitary tumors
Loeb, Lathrop (1919)	Prevented mammary tumors in mice by ovariectomy
Lacassagne (1932)	Induced mammary tumors in mice with pure estrogen
Nathanson, Andervont (1939)	Prevented mammary tumors in adult female mice with androgen
Huggins (1940)	Treated prostatic carcinoma in men by control of androgen
Woolley, Little (1943)	Noted sex organ development through adrenal compensation in castrated mice
Biskind, Biskind (1944)	Noted development of tumors in rat ovary transplanted to spleen
Hertz, Tullner (1948)	Demonstrated quantitative interdependence of hormones and a vitamin in tissue growth

* Material from Greenstein, J. P., *Biochemistry of Cancer.* New York, Academic Press, Inc., 1947.

The Rous agent, because of its rapid, apparently direct action, is particularly useful in studies of carcinogenesis. Effective methods for quantitative assay of the agent have been worked out by Bryan at the National Cancer Institute.[18] But a major obstacle remains—the lack of a method for extracting pure virus, needed for studies of mechanism. To develop such a method is a major objective in tumor virology today.

Now, in view of the fact that cancer research is ultimately concerned with human cancer, we may rightly ask: Why this deep interest in the virus tumors of animals? Simply because they offer valuable material for studies of carcinogenesis, which is probably a manifestation of the same intracellular derangement whatever the agent or species. In passing, let me emphasize that there is no accepted evidence of a virus cancer in man.

Table III lists some of the highlights of tumor endocrinology.* Pierre Marie, in associating a disease of endocrine origin with tumors of the pituitary, introduced a broad area of study and an important aid in cancer diagnosis. It was later established clinically that removal of an

* The material in this table, unless otherwise noted, is from Greenstein, *Biochemistry of Cancer.*[19]

endocrine gland tumor would often correct abnormalities of development.[20]—Through use of mice predisposed to mammary cancer, Loeb and Lathrop demonstrated a hormonal factor in carcinogenesis, placing tumor endocrinology on a sound experimental basis.—In connection with the next study listed, it should be mentioned that Allen and Doisy were the first to isolate a pure sex hormone.—Nathanson and Andervont, by injecting androgen, reduced the incidence of tumors in estrogen-developed tissues; and Nathanson, Haddow, Adair and others subsequently showed the value of steroid hormones in the treatment of breast cancer.

—This work of Huggins is a triumph of biochemistry as well as endocrinology. After appropriate preliminary studies on dogs, Huggins, Stevens and Hodges succeeded in controlling, at least in a limited way, prostatic cancer in men by means of castration or estrogen administration. Moreover, the acid phosphatase levels of the sera, as shown by the Gutmans and others as well as by Huggins, proved to be highly accurate indices of case progress. Most patients are improved, and many show marked and prolonged remissions of primary and metastatic lesions.

—In the next study listed, the castrated mice developed a high incidence of adrenocortical carcinoma.—In the next study, the tumors were attributed to stimulation of the ovary by pituitary hormone, an effect normally counteracted by estrogen, which in this case was inactivated in the liver.

—Hertz and Tullner, at the National Cancer Institute, have demonstrated that folic acid is required for normal growth response to estrogen, and that folic acid antagonists can inhibit growth of estrogen-stimulated tissues. Dietary manipulations produced a 40-fold differential in estrogen-induced growth of the chick genital tract.[21]

When viewed chronologically these isolated achievements elude interpretation. I believe, though, that the findings warrant the following generalizations: first, some tumors are functional with regard to hormonal production or response; second, tumors may be induced, prevented or controlled by hormonal manipulation; third, derangement of endocrine relations within the body may result in cancer; and fourth, tissue growth normally supported by hormones may be inhibited by antagonists. Thus the importance of endocrinology in the etiology, diagnosis, and treatment of cancer is plainly revealed.

Dietary manipulations have been shown to exert pronounced effects on carcinogenesis in animals. Caloric or amino acid restriction prevents or delays the appearance of a variety of tumors,[22] and choline deficiency, on the other hand, results in the development of hepatomas in the rat.[23] It is doubtful that these observations are of immediate practical value: the cancer-preventing diets abolish breeding capacity, and choline occurs in a wide variety of foods. As leads in cancer research, however, these and similar findings are highly encouraging and offer many suggestions for further studies. In one promising line of investigation, chemical carcinogens are administered to animals in conjunction with dietary manipulations, permitting precise control of two variables. In these studies the azo dyes are especially useful, since their action is known to be a function of diet.[24]

The effect of dietary alterations on human tumors already established has been relatively small in the few studies completed to date. In some animal experiments, however, alternate restriction and supply of a vitamin, such as riboflavin or pantothenic acid, has appreciably prolonged life, and further investigation is indicated.[25] Intensive studies on animals and selected cancer patients are needed before the role of nutrition in the control of cancer can be established.

In discussing the genetic influence in cancer, I will try to interrelate some of the material already published in this field. I believe that an understanding of the role of genetics in cancer must begin with a sound concept of the gene-character relation. Strictly speaking, a character, such as hair color, height, or color blindness, is not inherited. Its development is a result of the action of an inherited gene, or complex of genes, in a particular environment. The gene is a constant; the environment, a variable; the character, a product of the two. Stated otherwise, genes determine susceptibility to character formation; and with respect to cancer, may be said to establish, in every person, a threshold of susceptibility to the disease. The effective environment in character formation may include intra-uterine factors, diet, occupational influences—any condition, in fact, to which the individual is exposed; and it may include, secondarily, physiologic factors affecting cells. In plain words, then, cancer is not inherited, but a degree of susceptibility to it is.[26] And the adverse environment, whether that of the individual or a susceptible cell, is not beyond control.

The immediate questions confronting the geneticist in cancer re-

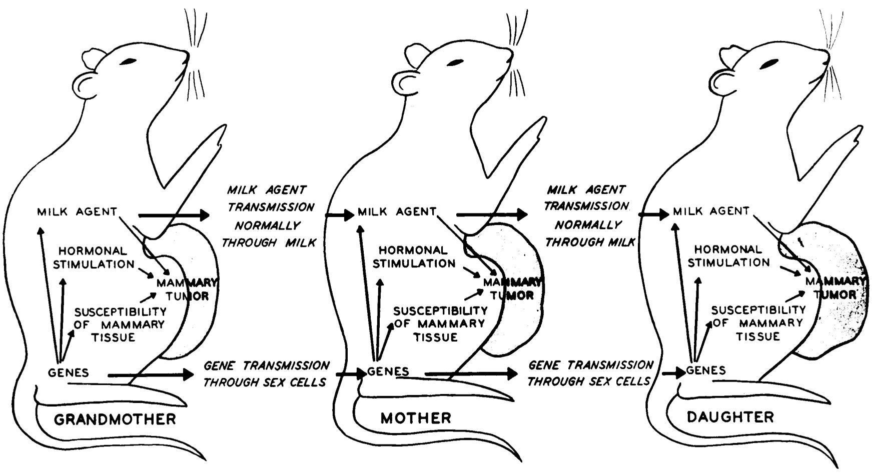


Figure 1—Relation of genes to other factors of mammary tumor development in the mouse

search are these: What are the genetic factors involved in carcinogenesis? To what environmental factors are they related? and By what physiologic paths do the genes function? For the most part, the problem is approached through studies with plants and lower animals, a practice well-grounded on the fact that the laws of genetics are among the most widely applicable in the field of biology. And of course the breeding rate must also be considered in studies involving several generations. An example of a lower form that has proved valuable as study material is the bread mold *Neurospora crassa*, which Beadle,[27] Tatum and others have used to disclose genetically controlled enzyme systems essential to the manufacture of protoplasmic constituents. Another useful species in cancer research is the common fruit fly [*Drosophila melanogaster*].

The most widely used subjects, however, are the mice of inbred strains, for which we are mainly indebted to the foresight of C. C. Little and the perseverence of L. C. Strong. Through inbreeding with selection over many years, geneticists have developed strains with high, predictable rates of cancer—mammary, lung, liver, etc.—and other strains in which tumors are infrequent. A high percentage of all cancer research requires these standardized experimental animals.

I have said that most cancers are not attributable to known carcinogens. This statement is more obviously applicable to tumors other than mammary that arise in these mice, whose external environment throughout life is apparently normal—that is, noncarcinogenic. We may assume that these mice have a high concentration of genes favorable to tumor development; but cancer is the product of genes and environment. How, then, can we explain that the over-all incidence of cancer in some strains may be higher than 80 per cent? Speaking generally, suspicion centers on the following possible environmental factors: one, a transmissible agent, of external or internal origin; two, a carcinogenic constitutional pattern, perhaps a result of intra-uterine effects on organization; and three, a combination of these.

Such a combination has been shown to constitute the effective environment in mammary tumor production in the mouse. Figure 1, prepared from material developed by Heston, represents the genes as determinants of the constitutional pattern as well as the susceptibility of the mammary tissue.[28] The cancer-predisposing constitution, in itself a product of genes and environment, operates in this case through hormonal stimulation of the tissue and propagation and transmission of the milk agent. It is highly encouraging that cancer in these mice, though the genetic influence is strong, can be prevented by foster nursing or endocrine control.

The question naturally arises, To what extent can these genetic findings be applied to cancer in man? On the basis of these and other studies, we can certainly say that hereditary factors are involved, and that these are related to environmental factors.[29] Perhaps our most important gain from this work is a conception of the probable nature of the carcinogenic influences in human cancer of unknown etiology.

We have all heard, but it bears repeating, that there is no evidence for a milk agent in human beings. Indeed, there is statistical evidence against it, in that studies have failed to reveal a higher incidence of breast cancer among the female ancestors of mothers than among those of fathers of breast cancer patients.[30] At present, practical application of our knowledge of the milk agent is not indicated. But the search for similar factors in human cancer must be continued.

Since man is not inbred, nor reared under laboratory conditions, one cannot predict—even if both parents have cancer of the same organ—whether the offspring will develop the disease. The genetic factors of most types of cancer are probably multiple. This and practical difficulties preclude eugenic control.[28] Further genetic studies, however, may disclose environmental and hereditary factors of cancer in man as they have in animals.

The development of genetically pure strains of mice, tumor transplantation techniques, and dependable means of inducing experimental cancer has made possible the productive application of biochemical methods in cancer research. In little more than a decade, biochemical analysis, performed against a background of biology, biophysics, pathology and other disciplines, has greatly contributed to an understanding of the properties of tumors and the tumor-bearing host. Whereas previous investigation was largely concerned with describing tissues in terms of composition, present biochemical studies emphasize the elucidation of tissue function—in a word, metabolism. And in view of the fact that cancer is a problem of growth, the importance of the new science in cancer research is manifest.

I shall attempt only to touch upon some of the major areas of activity in this field. Emphasis is placed upon those aspects of metabolism that would seem instrumental in the origin or maintenance of neoplasia: namely, enzyme activity, which underlies and effects the metabolic processes; protein synthesis, which in tumors is obviously excessive; carbohydrate utilization, which is glycolytic and hence supplementary; and the role of nucleic acid, which is associated with cellular reproduction.

With regard to enzyme activity, it may be said that every type of tissue is equipped with a characteristic pattern of enzymes, which serve as catalysts in metabolic reactions. The enzyme patterns of normal tissues are highly differentiated and vary markedly from one tissue to another. Greenstein has shown that in tumors, on the other hand, the patterns tend to be undifferentiated and nearly uniform, resembling those of the normal embryo.[6] This may explain how tumor tissue, though apparently devoid of a special 'cancer enzyme,' is geared for speed. Fundamental enzymology must be emphasized in any comprehensive program of cancer research.

In the study of tumor metabolism, untold possibilities are afforded by the recently developed techniques of tracing tissue components tagged with stable or radioactive isotopes. The major objective in tracer studies of protein synthesis is to explain the mechanism whereby substances that enter the metabolic processes are utilized in the formation of tumors. Normally, the ratio between the anabolic and catabolic processes of a given tissue bears an orderly relation to that of all other tissues. In cancer, on the other hand, this relation is disturbed. Is this the result of a deficient control mechanism, or of evasion of this mechanism through novel avenues of synthesis? If such avenues exist, tracer methods may reveal them. Then chemotherapeutic methods may be found to block them.

In the metabolic process whereby energy is derived from carbohydrate, cancer tissue, in contrast with resting nonproliferating tissue, represents a shift toward the anaerobic. In other words, the economy tends to be glycolytic, as in a cell whose oxygen or respiratory system is inadequate.[31] Warburg, the first to note this, ascribed it to a defect in the cancer cell.[32] In recent studies by Salter, Burk and others, the respiration rate of normal tissue slices increased far more than that of tumor slices when a suitable substrate, such as succinic acid, was supplied; and thus the tumor tissue was shown to have the lower oxidative capacity, confirming Warburg's interpretation. One is reminded that Warburg, in his classic studies, went another step and attributed cancer to interference with the respiration of growing cells.[32] But this is still an open question.

In recent studies by Hogeboom, Schneider and others, appropriate tests applied to cell fractions, isolated by centrifugation, demonstrated that essential respiratory enzymes, including cytochrome oxidase, are located on the mitochondria.[33]

It is interesting that these cytoplasmic particles, the mitochondria, undergo pathogenic mutation in plants,[34] show morphologic changes in tumors,[35] and contain nucleic acid.[36]

The following observations among others suggest a relation between nucleic acid and the origin and maintenance of cancer. All known duplicating units such as chromosomes, plastids and viruses contain ribose, desoxyribose or both kinds of nucleic acid in high concentrations; and ribose nucleic acid is high in certain cytoplasmic particles of virus size.[37] Moreover, studies such as those of Griffith and later Avery show that a nucleic acid is capable of invoking permanent cellular variations. In Griffith's experiment, one type of pneumococcus was transformed into another by contact with heat-killed organisms of the second type;[38] and Avery demonstrated that desoxyribose nucleic acid was the agent of the mutation.[39] Such observations suggest innumerable questions, of which a few may be raised in passing. What is the role of nucleic acid in the synthesis of protein? What is its role in cytoplasmic particles such as microsomes and mitochondria? Is nucleic acid the active principle of a cancer virus? Does alteration of nucleic acid represent the long-sought 'common denominator' of carcinogenesis? Only further, intensive investigation can provide the answers.

The research attack upon cancer is launched on two main levels: the gaining of basic knowledge, with a long view toward practical application; and the search for improved methods of prevention, diagnosis and treatment in the absence of an adequate explanation of the cancer process. In facing the cancer problem, we are encouraged by the fact that in many diseases the cause was unknown at the time the fight was won. I should like now to discuss briefly research in cancer therapy.

For the past three years we have heard a great deal about the therapeutic use of radio-isotopes. The isotopes most thoroughly tested against various forms of human cancer have been radioactive phosphorus [P^{32}] and sodium [Na^{24}], for whole-body radiation, and radio-iodine [I^{131}] for cancer of the thyroid. In leukemia, treatment with radio-phosphorus has produced less radiation sickness than X-ray, but has not proved superior in prolonging life.[40]

Before the radio-isotope can come into its own, means must be found for localizing these agents within the tumor, for the primary and metastatic cancer cells must receive many times as much radiation as the normal cells to warrant the treatment. Therapeutic doses must be administered with extreme caution. In several cases, such doses have been followed by aplastic anemia; and though insufficient time has passed to observe long-term effects, the dangers of radiation are well known. In clinical work involving localization of radio-isotopes in tumors, each treatment should be preceded by a small tracer dose, to determine whether adequate concentration in the tumor may be expected. Greater effort must be made to develop radioactive compounds with a high degree of tumor specificity. Until this is accomplished, the ultimate value of radio-isotopes in the treatment of cancer cannot be estimated.

During the late war, a class of compounds known as nitrogen mustards, which are closely related to mustard gas, were found to produce nuclear damage in cells. Subsequent investigation revealed that proliferating cells are most vulnerable.[41] From clinical data obtained so far, the nitrogen mustards seem to deserve a place in the treatment of

Hodgkin's disease, polycythemia, lymphosarcoma, and perhaps some cases of chronic leukemia. In these conditions, temporary remissions of varying duration have been observed. But it must be emphasized that these agents are highly toxic, and insufficiently selective to be curative. Other compounds within this class are being synthesized and tested.

Urethan [ethyl carbamate], long known as a hypnotic, has been found effective in chronic myelogenous leukemia and, to a lesser degree, in similar conditions.[42] In early cases, remissions lasting a few months may be obtained, but when the drug is discontinued, sudden relapse occurs. In advanced cases, this agent is inferior to radiation. I have mentioned that urethan induces pulmonary tumors in mice.

The compounds stilbamidine and pentamidine have been shown by Snapper and others to have some effect in multiple myeloma.[43] In conjunction with a low protein diet, these agents relieve pain and temporarily retard the disease. This is another indication that the cancerous cells most susceptible to damage are those of the blood or blood-forming organs.

In recent years a rational therapeutic principle has emerged from experiments with microörganisms—the principle of metabolite antagonism.[44] A *metabolite* may be regarded as a substance involved in the process of cellular growth and maintenance; an *antagonist*, a substance capable of interfering with the synthesis, utilization or function of a metabolite. An example of a metabolite is the vitamin folic acid; an antagonist to this, aminopterin. And under these definitions, one could include as metabolites the amino acids, enzymes and hormones. Several groups of compounds are being tested in laboratories and hospitals for possible antagonistic effect in the growth or maintenance of malignant cells.

In studies by Farber and others, folic acid antagonists have produced temporary remissions in a few children with acute leukemia.[45] At the National Cancer Institute, Law has obtained remissions in leukemic mice.[46] But these agents, too, are highly toxic, and are not recommended as yet for general use by the practitioner. Results to date, however, should encourage further investigation of these and other metabolite antagonists, especially in controlled experiments with animals. The underlying principle is sound and well worth pursuing.

I have mentioned the value of estrogen in the treatment of cancer of the prostate, and of androgen or estrogen in breast cancer. The

Therapeutic Trials Committee of the American Medical Association has undertaken the task of determining the optimal use of hormones in breast cancer therapy.[47] I shall not discuss the subject further, except to emphasize that to date hormonal treatment in cancer has been palliative only.

Another promising approach to the development of chemical agents for cancer therapy is the systematic screening of compounds known to damage cells. In this approach, it is initially recognized that the vulnerability of cancer tissue to an agent has always been shared by normal tissues. This is turned to advantage: known cytotoxic compounds are searched for those especially destructive to cancer cells; and as such agents are found, they are subjected to chemical modification designed to reduce toxicity or increase activity.

In a screening program under the direction of Shear at the National Cancer Institute, this is essentially the guiding principle in the selection of compounds for testing.[48] The workers represent a variety of scientific disciplines. Their concerted purpose is to find or develop chemical agents that either alone or combined with radiation or surgery will control tumors without prohibitive destruction of normal tissue.

Sarcoma 37 in the mouse is used in the preliminary screening of every compound. Transplanted tumors may be considered as artificially established, standardized metastases. Fifteen mice are used in the first testing of each agent.

So far, more than a thousand agents have been screened, and the results have far exceeded expectations. At a single dose near the lethal, definite tumor damage has been obtained in the last few years with about sixty compounds.[49]

Although none of the sixty positive compounds completely destroys the test cancer, the results show decided progress, not only in providing agents for further study but in proving the value of a screening method in experimental cancer chemotherapy. We propose to continue the screening procedure. Moreover, the positive agents will be tested against several forms of cancer in various laboratory animals. On the basis of findings to date, the structures of effective compounds are being studied in terms of function, with a view to producing, through alteration of the original molecule, an agent safe for the host but fatal to the tumor.

This brief review of studies in cancer therapy does not purport to reflect the large amount of effort invested in this field. I have tried only to indicate that there is such an effort, and to emphasize, to my deep regret, that no cure except surgery or radiation is as yet available. This is not to say, however, that highly encouraging results are lacking. In this difficult problem, we now appreciate that a concerted attack, based on sound scientific principles and following practical systematic lines of approach, is our best assurance of success. In laboratories and hospitals throughout the country, such an attack is under way.

Another approach that has yielded valuable information and is being intensified in cancer research programs is epidemiology. This term is used to designate investigation of the incidence of cancer by types and site with relation to total history including environment. This extension of the term 'epidemiology' is largely due to similarities of method to those used in the study of communicable disease. In cancer research, epidemiologic methods have contributed especially to our knowledge of causal factors in the environment of industrial workers.

Studies to identify environmental factors of carcinogenesis in industry and to develop means of controlling them usually proceed in four major steps. First, mortality rates by geographic region are searched for areas of high incidence. Second, the hazardous areas are searched for evidence of possible carcinogens, such as unusual industrial products. Third, the suspected agent is tested in the laboratory. If found carcinogenic, the fourth step is taken: measures are devised for protecting the workers and community. These steps, though not always applied in formal programs, have exposed a formidable host of carcinogenic agents and influences, including the following industrial materials: tar, shale oil, crude paraffin, creosote, crude anthracene, arsenic, benzol, chromates, asbestos, intermediates of aniline dyes, and the energy agents already mentioned.[50] At the National Cancer Institute, a program under the direction of Hueper has been established to detect other agents and to advise and assist industries in eliminating the hazards.

Another epidemiologic approach is to follow special population groups, in order to determine whether certain influences, such as a given diet or habit, will contribute to carcinogenesis. A familiar example of a habit that leads to cancer is the chewing of betel nut quids in Asiatic countries.[50] At present, strong clinical impressions indicate that groups with certain pathologic conditions, such as achlorhydria and pernicious anemia, should be traced with a view to deciding whether the incidence of cancer in these groups is higher than average. A major advantage of such a program is the contribution to early case finding.

In coöperation with the University of Washington in Seattle, the National Cancer Institute is engaged in laboratory and clinical studies to develop a diagnostic test or tests for cancer. At present, tests reported in the literature are being evaluated through application to cancer patients and persons with other diseases. Coöperative arrangements have been established with local hospitals and physicians. Tests found effective on the advanced cancer patients in Seattle will be tried for mass-screening possibilities at the venereal disease clinic of the United States Public Health Service Medical Center in Hot Springs, Arkansas. The possibility that available material would yield a practical means of segregating persons for further examination should be thoroughly explored.

In this discussion I have not attempted to divide the subject matter by scientific disciplines, since cancer research, for the most part, is conducted on an 'interdisciplinary' basis. This tendency to transcend departmental barriers represents an important advance. In the past, outstanding contributions were made in isolated fields, such as pathology, physics and surgery, to which must be credited, respectively, microscopic examination of tissue, which remains the most reliable method of cancer diagnosis, and radiology and radical excision, the only cures. Now that a groundwork has been laid, however, those disciplines are drawn upon by others, which build in turn an indispensable foundation.

A voice from antiquity bespoke the interdisciplinary approach: Bacon said: "The strength of all sciences, which consists in their harmony, each supporting the other, is as the strength of the old man's fagot in the band; for were it not better to set up one great light, or branching candlestick of lights, than to go about with a small watch candle into every corner?" James Ewing was among the first to conceive of a cancer institute in the modern sense—as an institution where scientists of many disciplines combine their efforts and resources in a common mission, cancer research. In the future an even closer integration of disciplines must be achieved.

Integration of laboratory and clinical investigation in cancer is requisite throughout the country. At the National Institutes of Health, this need will be met with the completion of the new Clinical Center, in which 100 beds will be used for cancer patients. Ground is now being prepared for the buildings, which are expected to be completed in about two years. The Center will make possible direct application of basic findings, and will help meet the national need for clinical cancer studies.

This general view of cancer research may warrant a general conclusion. From the facts gleaned in recent years, through much profound thought and unremitting toil in laboratories and clinics throughout the world, one may deduce that cancer, contrary to the word of some discouraged early workers, is not an unsolvable mystery of the universe. It is a practical scientific problem, and science in its stride can conquer it. But the problem, I repeat, is subtle; the solution may not come soon; and the attack, at least for the present, must include much basic investigation and must advance on a broad front.

I should like to close on a note of caution. The people of the world have a vital stake in the progress of cancer research, and are entitled to full and fair reports of scientific accomplishment. Because of the great eagerness of the public for news that cancer research is 'on the right track,' that the long-sought cure is at hand or close to it, reports of moderate advances are frequently exaggerated. Because the wish is father to the thought, hopeful new leads may be mistaken for fully developed answers to major questions.

The penalty of exaggeration is disillusionment. Our outlook in cancer research is optimistic; all of us hope that the solutions to the problems are not too far off, and there is no reason to believe that they are. But the available evidence does not necessarily indicate that the solutions are right around the corner. The distance ahead, as well as a balanced interpretation of achievements, must be emphasized in every progress report.

A concerted attack on cancer is being made today through the efforts of universities, general and cancer hospitals, voluntary organizations such as the American Cancer Society, and of Federal agencies such as the National Cancer Institute and the Atomic Energy Commission. Through continued support of these efforts as long as necessary, by a generous and confident nation, the cancer problem will be solved.

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